REMARKS/ARGUMENTS

Claims 1, 3, 5-7, 11, 12 and 19 are pending in the above-captioned application. Claims 1, 3, 5-7, 11, 12 and 19 stand rejected under 35 U.S.C. 103 (a) as being unpatentable over Unger, U.S. Patent No. 6,033,645. Claim 1 has been amended to more particularly claim the instant invention. Applicant respectfully submits that the amendments do not incorporate new matter in contravention of 35 U.S.C. §132. The following remarks are believed to be fully responsive to the Office Action.

THE REJECTIONS UNDER 35 U.S.C. § 103

SHOULD BE WITHDRAWN

Claims 1, 3, 5-7, 11, 12 and 19 rejected under 35 U.S.C. 103 (a) as being unpatentable over Unger, U.S. Patent No 6,033,645 ("Unger"). In response, Applicants submit that each of the rejections should be withdrawn for the reasons stated below.

The present invention claims a method of administering a gas-containing contrast agent to a subject by continuous infusion. The contrast agent is administered by continuous infusion over an infusion period of 5-60 minutes, and is delivered from the upper extremity of an essentially vertically positioned syringe and is admixed with a flushing medium prior to administration to the subject. Claim 1 has now been amended to clarify that the gas-containing contrast agent is admixed with the flushing medium, and that the admixed product is administered over a period of 5-60 minutes. Hence, both the contrast agent and the flushing medium are administered over a period of 5-60 minutes. Basis for the amendment is found throughout the specification using the term "admixing prior to administration", and e.g. in the Examples 1-6 and 7-14, Tables 1 and 2 wherein different infusion times are exemplified. The preamble of claim 1 has further been amended to a "method of administering a gas-containing contrast agent", at the same time as the previous preamble "enhancing product homogeneity" has been included as an actual step in claim 1. Basis for the new preamble is e.g. found on page 5, lines 9-17, of the PCT specification and basis for

the "enhancing product homogeneity" is e.g. found on page 4, lines 9 to 32, of the PCT specification.

As stated earlier, the present invention has identified a solution to a problem associated with the administration of a gas-containing contrast agent to a subject by infusion. A problem with the continuous infusion of gas-containing diagnostic contrast agents over a long period arises from the tendency of gas-containing components to float, since this will lead to inhomogenities forming within vessels, such as power-driven syringes, which may be used to administer the contrast agent. This may, for example, lead to an increase in microbubble concentration in the upper part of such a vessel and/or to changes in size distribution occurring at various points within the vessel as larger microbubbles float more rapidly than smaller microbubbles. This problem increases with increased time of administration of the contrast agent. The Applicant has surprisingly found that by combining delivering of the contrast agent from the top of a vertically positioned syringe and admixing this with a flushing medium, prior to administration to a patient, and deliver this admixed product to the patient over a period of 5-60 minutes, the segregation is minimized and enhanced product homogeneity is achieved. By using a syringe as the delivery reservoir and placing this in a vertical position, with the outlet pointing upwards, the effects of floatation separation is greatly reduced, as further explained in the specification on page 3 and 4. The admixing with a flushing medium further enhances the homogeneity of the contrast agent that is delivered to the patient, e.g. by reducing the residence time of the agent in connecting tubes etc. It is further preferred that the syringe is positioned so that the bulk flow direction of the gas-containing contrast agent during expulsion is the same as the direction of segregation of the dispersed gas-bubble phase, i.e. upwards, since this will assist in counteracting the formation of concentration gradients of the dispersed gas-bubbles during administration. The claimed invention hence provides a method of administration wherein enhanced product homogeneity is achieved by combining the features of delivery of the contrast agent from the upper extremity of a vertically positioned syringe, and admixing this with a flushing medium prior to administration, and administer the admixed product to a subject over a period of 5-60 minutes.

Unger discloses ultrasound contrast agents and delivery of such to a patient. Unger is aware that the quality of images generated using contrast agents are dependent of the concentration of the contrast agent in the region being imaged. An excess or insufficient concentration of contrast agent can cause diagnostic artifacts, such as shadowing and darkening or lightening of the image. The problem of Unger is to administer a contrast agent to a patient and generate an image without artifacts. The invention of Unger is hence directed to methods for controlling and or regulating the concentration of a contrast agent at a region of interest. To control and regulate such concentration Unger reports that the rate of administration of the contrast agent may have a profound effect on the quality of the resulting diagnostic images (column 44, lines 22-60). The contrast agent of Unger is typically administered over a period of 5 seconds (column 45, line 20), or up to a period of 50 seconds (column 3, line 55), and any subsequent flush is typically administered over a period in the range 10 seconds to 10 minutes. To promote the transport of the contrast agent from the injection site into the bloodstream, a flush may be administered to push or wash the contrast agent into the bloodstream (page 70).

Unger discloses a different problem than the problem of the current invention. The problem of Unger is to avoid artifacts in an image. His solution to this problem is to control the rate of administration of the contrast agent. The motive for controlling the administration rate and period is hence different from the motive of the present invention. Although Unger disclaims any specific rates to be the exhaustive rate limitation, there is neither no indication or motivation by Unger that a contrast agent could be administered to a subject over such long period as up to 1 hour, nor that such administration should be admixed with a flushing medium over the same perdiod. To avoid artifacts in the image Unger clearly suggests to administer the contrast agent over a period of seconds.

Further, there is no teaching by Unger that the syringe should be positioned vertically for upright delivery of the ultrasound contrast agent, combined with that the contrast agent should be admixed with a flushing agent prior to administration. There is further no teaching

or indication by Unger that the administration direction of the contrast agent should be linked to the segregation direction of the contrast agent components.

The Examiner states that the fact that applicant has recognized another advantage than Unger, which would flow naturally from the suggestions of the prior art cannot be basis for patentability. The Applicant respectfully submits that the skilled in the art reading Unger, could optimize the rates of administration and achieve optimal images without artifacts. However, Unger does not provide any motivation for the skilled man to modify the teaching of this reference to a method of achieving enhanced product homogeneity in infusion administration of a contrast agent over a period as long as up to 1 hour. Further, there is no reasonable expectation of success in achieving enhanced product homogeneity in infusion administration of a contrast agent over a period as long as up to 1 hour by modifying Unger. One example wherein Unger actually discourage one of ordinary skill in the art to modify duration of the infusion is given in column 48, last paragraph and column 49 first paragraph wherein an embodiment including flushing is elaborated. Unger suggest that the flush medium is administered over a period of 10 seconds, and suggests rates of from about 0.02 to 2.3 ml/sec. If this was to be administered over a period of one hour a total amount of maximum 8280 ml flushing medium would be given, which would be intolerable. The flushing used by Unger is hence clearly meant to push or wash the contrast agent into the bloodstream, and is administered over a short period, and one of ordinary skill in the art would not suggest to prolong such flushing over such a long period as one hour.

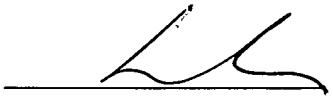
It is therefore respectfully submitted that 35 U.S.C. 103 rejections of claims 1, 3, 5-7, 11, 12 and 19 over Unger be withdrawn.

CONCLUSION

In view of the amendments and remarks herein, applicants believe that each ground for rejection or objection made in the instant application has been successfully overcome or obviated, and that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and objections, and allowance of the current application are respectfully requested.

The Examiner is invited to telephone the undersigned in order to resolve any issues that might arise and to promote the efficient examination of the current application.

Respectfully submitted,



Li Cai
Reg. No. 45,629

GE Healthcare Inc.
101 Carnegie Center
Princeton, NJ 08540
Phone (609) 514-6418

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